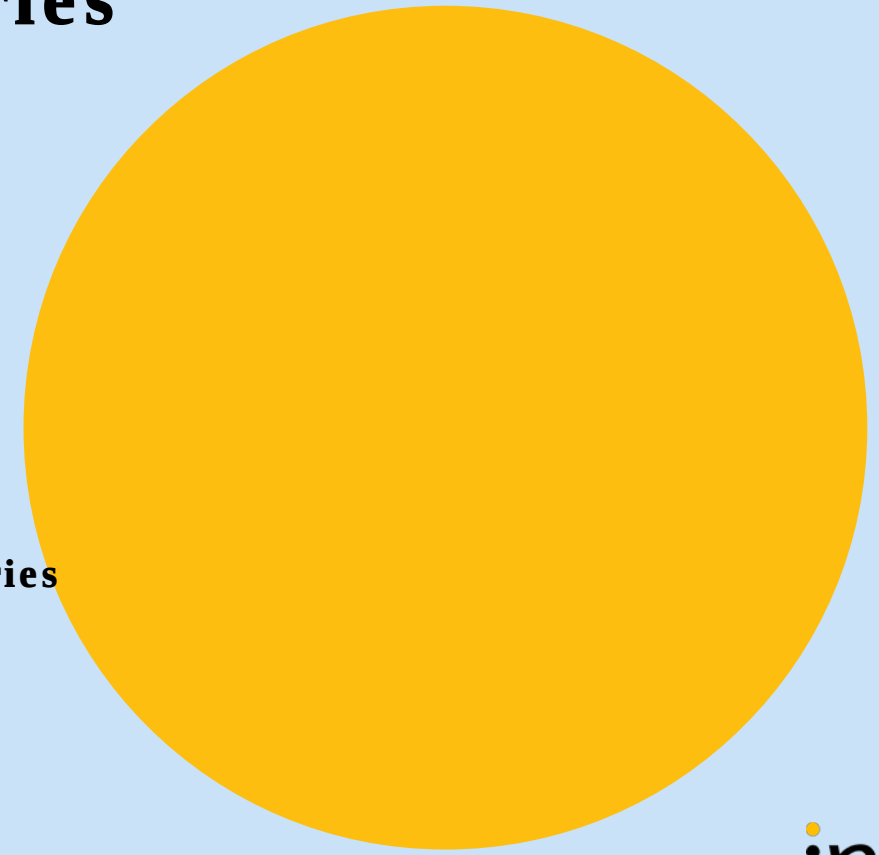
Multi-product registries



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FDA Public Meeting: Pregnancy Registries

28 May 2014

inc Research

Disclosure

- I am a salaried employee of INC Research, LLC, a contract research organization (CRO), which conducts post-approval studies under contract with pharmaceutical companies, including but not limited to assessments of fetal exposures during pregnancy to drug and biologic products.

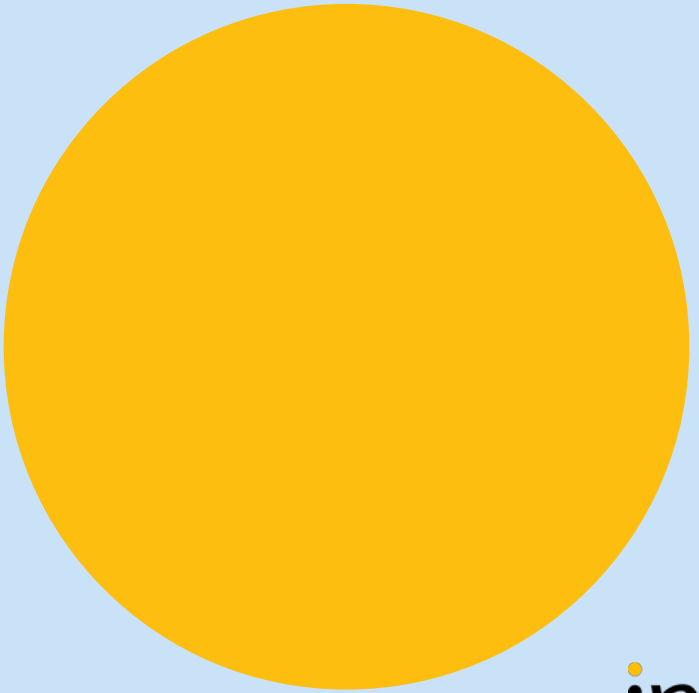
Background

Fact	Most information on the safety/risk of drugs related to pregnancy is collected after the drug has been approved and used intentionally or unintentionally by pregnant women in the real world.
Fact	Pregnancy registries are generally implemented when there is either a safety concern, an indication for use during pregnancy, or a high likelihood of use in women of reproductive age.
Fact	The purpose of pregnancy exposure registries is to provide human data on the safety/risk profile of pharmaceutical products during pregnancy.
Fact	In order to fulfill the goal of informing the decisions of patients and health care providers, it is imperative to initiate the registry as soon as possible using the most effective design strategy.

Objectives

- Differentiate single vs. multi-product or disease based registries
- Demonstrate the appropriate use of each with examples
- Discuss advantages, challenges and special considerations
- Delineate perceived barriers to implementation

Definitions and examples



Product versus disease registries

- Product registry
  - Eligible population is identified based on exposure
    - Drug
    - Biologic
    - Medical device

- Disease registry
  - Eligible population is identified by common condition or diagnosis
    - Treated or untreated
    - Therapy may include one or several different drug products

Single product registries

- What are they?
  - A registry for a single drug / biologic product
    - Multiple formulations, varying doses, different routes of administration
    - Brand and generic versions

- When are they appropriate?
  - Newly approved product
  - First product in a new drug class
  - New indication for a marketed product
  - High likelihood of use in women of childbearing potential
  - Product approved for use in a unique population
  - Product with known pregnancy and/or fetal risks
  - Product with excess risk compared to other treatment options for a given condition

Single product registries

Examples

Registry	Disease or condition	Product
Ribavirin Pregnancy Registry	Hepatitis C	Ribavirin
Adenovirus Pregnancy Registry	Adenovirus	Adenovirus vaccine

Ribavirin Pregnancy Registry - http://www.ribavirinpregnancyregistry.com

Adenovirus Pregnancy Registry - http://www.clinicaltrials.gov/ct2/show/NCT01584037

Multi-product registries

Simple scenario

- What are they?
  - A registry for multiple different products for the same indication from a single pharmaceutical company

- When are they appropriate?
  - Products are within a single drug class
  - Products have a similar risk profile
  - Products likely to be used in the same patient population
  - Concomitant exposures are concerning
  - Operationally and logistically feasible

Multi-product registries

Simple scenario examples

Registry	Disease or condition	Number of products
Sumatriptan/Naratriptan/Treximet Pregnancy Registry	Migraines	3
MotHER Pregnancy Registry	HER2+ breast cancer	3

Sumatriptan/Naratriptan/Treximet Pregnancy Registry – http://pregnancyregistry.gsk.com/documents/SumNarTrex_InterimReport_2012.pdf

MotHER Pregnancy Registry – http://www.herceptinpregnancyregistry.com/index.htm

Multi-product or disease based registries

Complex scenario

- What are they?
  - A registry for all marketed brand and generic products used to treat a particular condition

- When are they appropriate?
  - Products are manufactured in combination
  - Complex multi-drug treatment regimens
  - High likelihood of polytherapy
  - Frequent new product approvals
  - Internal comparisons are desirable
  - Confounding disease or population characteristics may exist

Multi-product or disease based registries

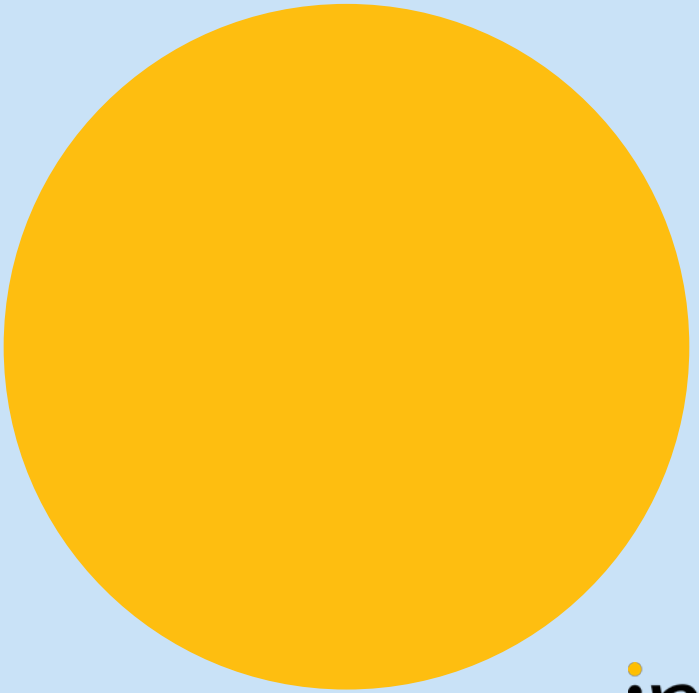
Complex scenario examples

Registry	Disease or condition	Type of products	Number of products
North American AED Pregnancy Registry	Epilepsy	Anticonvulsants	38
Antiretroviral Pregnancy Registry	HIV Hepatitis B	Antiretrovirals Antivirals	38

North American AED Pregnancy Registry – http://www2.massgeneral.org/aed/index.htm

Antiretroviral Pregnancy Registry – http://www.apregistry.com/Default.aspx

Case study: The Antiretroviral Pregnancy Registry



Case study

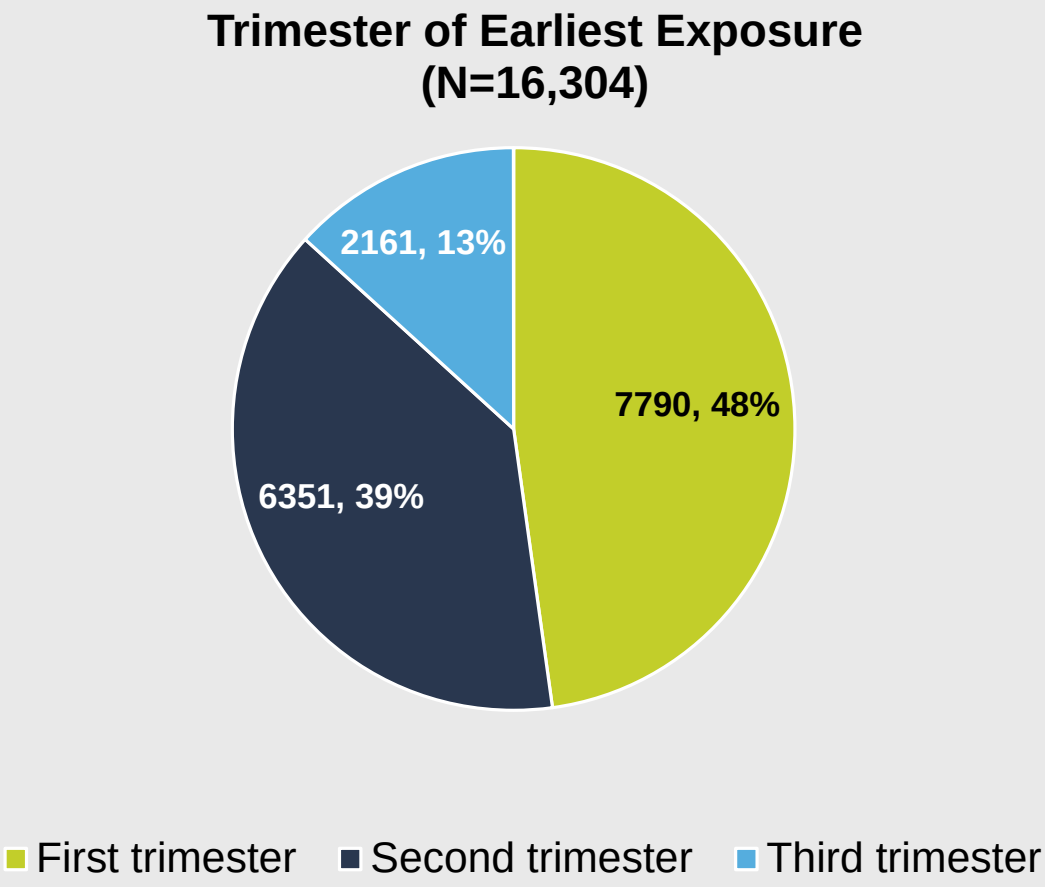
The Antiretroviral Pregnancy Registry

Metric	July 31, 2013
Prospective enrollments	18,488
Countries reporting	67
U.S. enrollments	78%
Lost to follow-up	9.5%

- Currently there are:
  - 38 drugs being monitored
  - 23 participating manufacturers

Case study

The Antiretroviral Pregnancy Registry



Case study

The Antiretroviral Pregnancy Registry

Results of prospective enrollments with outcome as of July 31, 2013:

Number of Outcomes	16,589
Number of Live Births	15,451
Number of Defect cases[1]	445

95% CI for Prevalence of Birth Defects for Exposures in:

1st Trimester	201/6,926	(2.9%)	2.5% - 3.3%
2nd/3rd Trimester	242/8,523	(2.8%)	2.5% - 3.2%
Any Trimester	445/15,451	(2.9%)	2.6% - 3.2%

Risks of defects for 1st trimester relative to 2nd/3rd trimester : 1.02 (0.85, 1.23)

[1]Defects meeting the CDC Criteria only. Excludes reported defects in pregnancy losses <20 weeks. An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion. Note: Due to unknown trimester of exposure data for 2 case(s) with birth defects, the specific counts may not sum to the overall total.

Case study

The Antiretroviral Pregnancy Registry

Regimen	Defects/Live births	Prevalence (95% CI)
Lamivudine	136/4360	3.1% (2.6%, 3.7%)
Zidovudine	129/4000	3.2% (2.7%, 3.8%)
Ritonavir	52/2260	2.3% (1.7%, 3.0%)
Tenofovir	46/1982	2.3% (1.7%, 3.1%)
Emtricitabine	34/1400	2.4% (1.7%, 3.4%)
Nelfinavir	***47/1211***	***3.9% (2.9%, 5.1%)***
Lopinavir	26/1125	2.3% (1.5%, 3.4%)
Nevirapine	31/1061	2.9% (2.0%, 4.1%)
Abacavir	27/905	3.0% (2.0%, 4.3%)
Atazanavir sulfate	19/878	2.2% (1.3%, 3.4%)
Stavudine	21/805	2.6% (1.6%, 4.0%)
Efavirenz	18/766	2.3% (1.4%, 3.7%)
Didanosine	***20/416***	***4.8% (3.0%, 7.3%)***
Indinavir	7/289	2.4% (1.0%, 4.9%)
Darunavir	5/212	2.4% (0.8%, 5.4%)

Case study

The Antiretroviral Pregnancy Registry

Advisory Committee Consensus:

In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the Registry finds no apparent increases in frequency of specific defects with first trimester exposures and no pattern to suggest a common cause. The Registry notes modest but statistically significant elevations of overall defect rates with didanosine and nelfinavir compared with its population based comparator, the MACDP. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counseling patients. However, potential limitations of registries such as this should be recognized. The Registry is ongoing. Health care providers are encouraged to report eligible patients to the Registry at www.APRegistry.com.

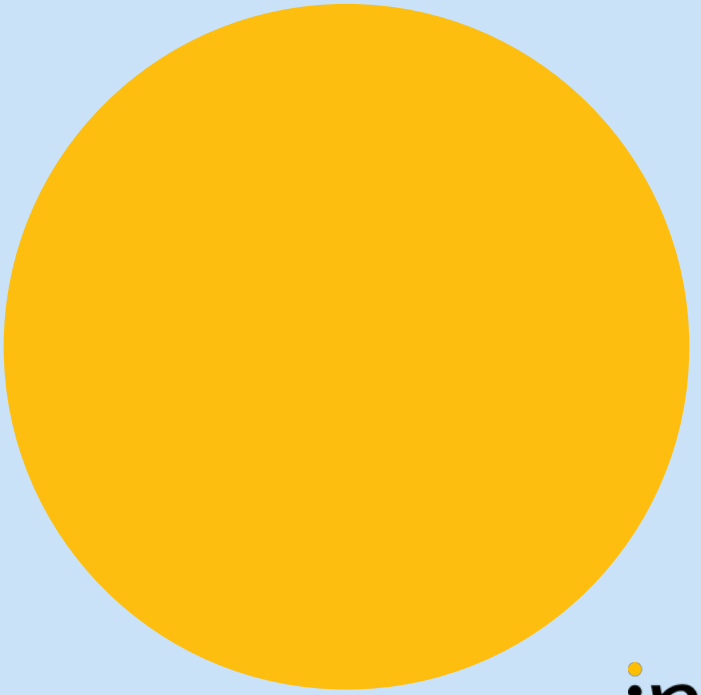
Case study

The Antiretroviral Pregnancy Registry

- **Disclosure:** The APR is funded by AbbVie, Apotex Inc, Aurobindo Pharma Ltd, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Cipla Ltd, Gilead Sciences Inc, HEC Pharm, Hetero Labs Ltd, Hoffman La-Roche, Janssen R&D Ireland, Lupin Pharmaceuticals Inc, Merck & Co. Inc, Mylan Laboratories, Novartis Pharmaceuticals, Pfizer Inc, Prinston, Ranbaxy Inc, Sciegen Pharmaceuticals Inc, SigmaPharm Laboratories, Strides Arcolab Ltd, Teva Pharmaceuticals, and ViiV Healthcare (represented by GlaxoSmithKline)

- **Acknowledgement:** The APR acknowledges the outstanding efforts of all of the clinicians submitting cases, as well as the valuable contributions of the Steering Committee

Advantages and challenges



Multi-product or disease based registries

Advantages

- Logical
  - Avoid duplicated efforts
  - Reduces population overlap
- Economical
  - Pool resources and budgets from multiple stakeholders
- Efficient
  - Budget
  - Resource
  - Expertise
- Methodological
  - Standardized data collection, assessments and analysis
  - Enhanced validity and power

Multi-product or disease based registries

Advantages

- Recruitment
  - Reduced competition
  - Robust awareness efforts

- Clinical
  - Centralized resource for patients and physicians
  - Minimize health care provider burden
  - Increase incentive to participate
  - Coherent assessment of available data
  - Consistent message safety/risk profile

Multi-product or disease based registries

Challenges

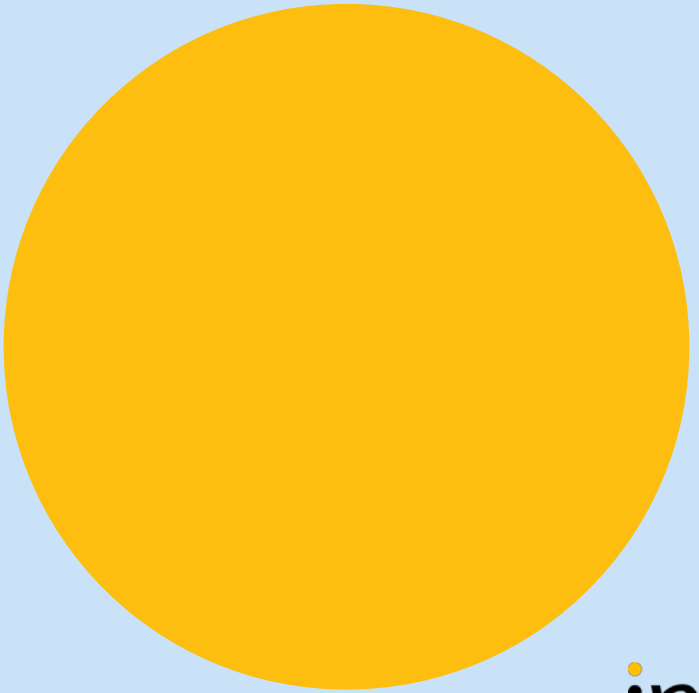
- Complexity
- Collaboration
- Communication
- Competition
- Confidentiality
- Commitment

Multi-product or disease based registries

Analytic considerations

- Analyses
  - Individual drug
  - Drug class
  - Monotherapy versus polytherapy
  - Overall registry
- Comparison group
  - Background reference group(s)
  - Internal comparison group(s)
- Potential for confounding / bias
  - Confounding by indication
  - Channeling bias

Special considerations



Special considerations

- Early planning
- Governance structure
- Alignment of objectives
- Perceived barriers

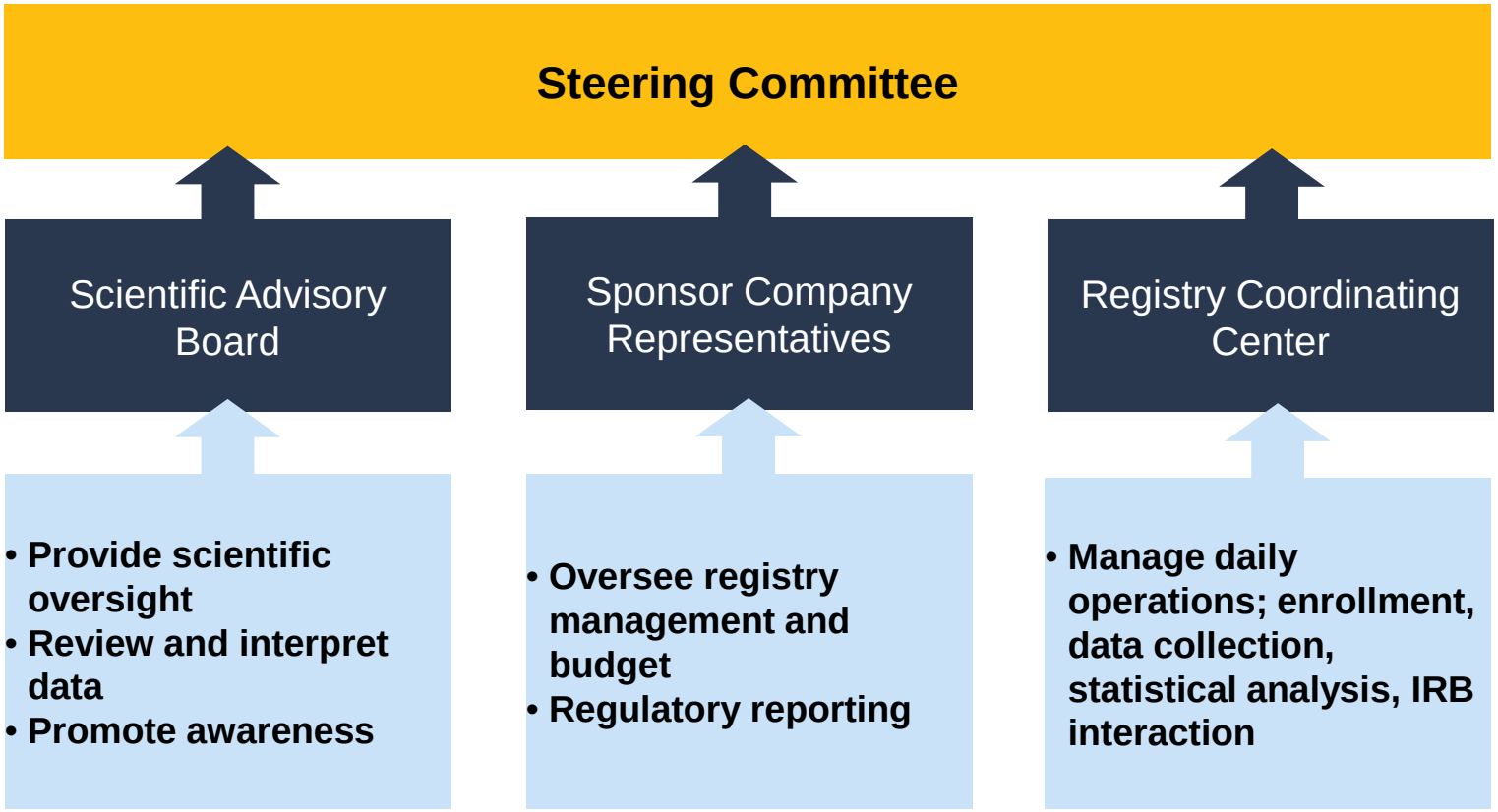
Special considerations

Early planning

- Registries require unique approaches in the design, data collection, statistical analysis, and reporting and dissemination of data.
- Special attention needs to be given to:
  - Subject recruitment and retention
  - Privacy issues
  - Regulatory requirements
- Early planning allows for:
  - Coordination of resources for increased utilization and efficiency
  - Standardization of data elements
  - Enhanced comparability
  - Datasets to be joined or linked in the future

Special considerations

Governance structure



Special considerations

Aligning objectives

Business objectives

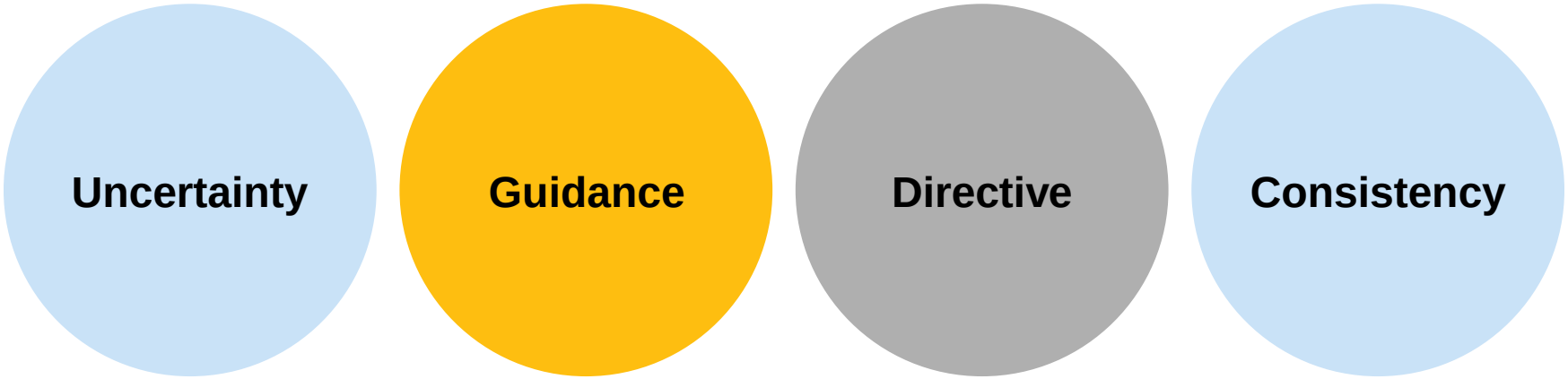
- Market/claim support
- Increase physician and patient awareness of disease and treatment options
- Satisfy post-approval regulatory commitments
- Support risk management strategies
- Product differentiation/positioning in competitive market
- Reinvigorate older brands
- Engage with key academic opinion leaders, prescribing physicians, and community disease advocacy groups

Scientific objectives

- Determine product effectiveness
- Establish product safety
- Demonstrate product cost/benefit
- Measure patient/physician satisfaction and/or impact on QoL
- Describe utilization patterns and patient compliance
- Document natural history of disease and identify predictors of outcomes
- Generate hypotheses for future studies

Special considerations

Perceived barriers to implementation



Conclusions

Implementation of an effective pregnancy registry hinges on identifying the most appropriate design

Expert consultation is a critical step in understanding the regulatory landscape and drug or population specific nuances

Engage stakeholders to gain broad participation and plan early to ensure the greatest utility is realized

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